Title: Correlates of fatigue among South African adolescents living with HIV and receiving antiretroviral therapy

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Compliance with Ethical Standards

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Abstract

Background: Fatigue among adolescents living with HIV is poorly understood. In this study, we examined the relationships between fatigue and demographic and psychosocial variables to further the understanding of the symptom experience and associated factors.

Method: We recruited consecutive attenders at ART clinics in the Western Cape, South Africa (N = 134, age 11-18 years). Participants completed a battery of questionnaires, including measures of fatigue, insomnia and mood disturbance.

Results: Just under a quarter (24.6%) of adolescents reported elevated levels of fatigue that affected their functioning. The linear combination of age, depression, and insomnia explained 40.6% of the variance in fatigue.

Conclusion: Amongst adolescents with HIV, fatigue seems a problematic symptom associated with poor sleep and mood disturbance. Timely identification and management of these potentially disabling symptoms are needed to attain better health outcomes and retention in care in this group. Interventions aimed at ameliorating these symptoms are needed.

[149/150 words]

Keywords: *Fatigue, HIV, adolescent, antiretroviral therapy, South Africa*

Introduction

Globally and in South Africa, adolescents continue to be at substantial risk of HIV infection. The most recent estimates suggest that more than 2 million adolescents (10-19 years old) were living with HIV globally, of which 250 000 were newly infected (1). With the introduction of antiretroviral therapy (ART), morbidity and mortality rates, as well as rates of disease progression have substantially decreased (2,3). As such, HIV has now for many years been considered a treatable condition, rather than a terminal diagnosis. While ART is able to reduce HIV replication in the blood and limit disease progression (4), the treatment does not relieve (and may even exacerbate) the numerous disabling symptoms associated with living with a chronic illness like HIV. Amongst these disabling symptoms is fatigue. Between 33% and 88% of adults living with HIV experience elevated fatigue (5,6), which is reportedly present through all stages of disease progression (7) and if left untreated, may become more pronounced overtime (6). Similar rates of fatigue are reported amongst adolescents in South Africa (about 24.6% using the Chalder Fatigue Questionnaire (CFQ)) (8).

Fatigue is known as extreme tiredness resulting from mental or physical exertion or illness, leading to a decrease in the capacity to perform physical and/or mental activities (9). When fatigue persists for at least a month, is not relieved by rest and impacts on functioning, it is considered to be ‘chronic fatigue’ (9,10). In a previous paper we showed that adolescents living with HIV experience fatigue as problematic, and perceive it to have a considerable impact on their daily lives, including their ability to concentrate at school, and socialise with peers (11).

In adults living with HIV, various correlates of fatigue have been examined, including biological markers such as CD4 count and viral load, sociodemographic

factors such as age, gender, and income and psychosocial factors such as depression, anxiety and insomnia (see Table I). Despite a fairly substantial literature on correlates and predictors of fatigue in adults, less is known about the correlates of fatigue among adolescents living with HIV.

<Insert table I about here>

The symptom management model (9,12) is an evidence based theoretical model that has been applied to the symptom of fatigue among HIV in adults, and may be a useful way to conceptualise fatigue in adolescents with HIV (13). It postulates that an individual's experience of their symptoms (e.g. fatigue), the things they do to manage these symptoms (e.g. adhere to an ART regimen), and the potential outcomes of symptoms (change in severity, frequency or duration) are inter-related. Individual variables (e.g. demographic factors, psychological factors, and developmental stage), the environment (e.g. social and cultural factors) and illness and health related factors (e.g. health status or type of disease) also influence symptom management. Understanding more about chronic fatigue in adolescents living with HIV, and identifying factors associated with it in this population would enable the timely identification and treatment of it, leading to potential remediation.

Chronic fatigue is potentially a prominent and disabling symptom among adolescents living with HIV. Fatigue is one of the most disabling symptoms amongst adults living with HIV, and a failure to ameliorate these symptoms has been shown to impact on quality of life (14,15) and decrease functional ability(14,16). Children and adolescents living with HIV face unique challenges throughout their life course. Indeed, adolescents have a lifelong journey with HIV and ART, and quite possibly

with concomitant fatigue. However, the limited empirical investigation of fatigue in this population means that it continues to be poorly understood and relatively neglected. Based on evidence in adults with HIV, we hypothesised that age, female gender, anxiety, insomnia and depression, would be associated with fatigue. This study explored the correlates and predictors of fatigue among HIV-infected adolescents in the Western Cape of South Africa.

Methods

Participants

Participants were 134 adolescents living with HIV, aged 11 – 18 years. Males (N = 56) and females (N = 78) were included. Participants were recruited from community clinics or infectious diseases clinics where they were enrolled in an ART programme. To be eligible to participate in the study, participants had to be sufficiently competent in either Afrikaans or English. Clinic staff at both sites referred participants to our study. Adolescents were not referred for participation (and subsequently excluded) by clinic staff if they presented on the day with significant developmental delay, were in need of emergency medical assistance, or had a severe psychiatric illness (e.g. florid psychotic symptoms).

Procedure

Consecutive clinic attenders who were potentially eligible to participate were briefly informed about the study by clinic staff during their follow-up appointments at an ART clinic or hospital site. If they were willing to consider taking part, the clinic staff referred them to a research assistant (SdT). The research assistant met with them in a private room and explained the study to them in greater depth.

Participation was voluntary and participants could withdraw from the study at any time without consequences for their treatment. Those who agreed to participate were asked to complete a consent form. After providing written consent, participants completed a battery of questionnaires that were available in either Afrikaans or English. If a participant was unable to understand the questionnaire items, they were helped by the research assistant. Participants were given a mobile phone top-up voucher and refreshments as a token of appreciation for their participation in the study.

Measures

Demographic questionnaire: Participants completed a demographic questionnaire that captured information on gender, age, ethnicity, social class (lower -, working - or middle class) and employment status.

Fatigue: The 11-item Chalder Fatigue Scale (CFQ) (17) assesses the severity of physical and mental fatigue over the last month. Each item is rated on a 4-point scale, ranging from 0 (less than usual) to 3 (much more than usual). Scores were summed, with a maximum total score of 33. A total score of ≥18 is an indication of problematic levels of fatigue in adults (18), and has been widely applied in studies of fatigue in adolescents (19). The CFQ had high internal consistency in our sample, with an alpha coefficient of 0.83.

Insomnia: The 8-item Athens Insomnia Scale (AIS) assesses sleep disturbances over the past month. It includes problems with sleep induction, awakening during the

night, sleep duration, sleep quality, well-being, mental and physical functioning, and daytime sleepiness. In Chinese adolescents, a score of ≥7 was found to be optimal for establishing sleep disturbance (20). The AIS had a high internal consistency in this sample, with an alpha coefficient of 0.82.

Depression: The 10-item depression subscale of the Revised Children's Anxiety and Depression Scale (RCADS) is validated for children and young people aged 7-18 years (21). The items assess various symptoms of depression, including: feeling sad or empty, anhedonia, trouble sleeping, change in appetite, lack of energy, disturbance in cognition, feelings of worthlessness, lack of desire to participate in activities, and restlessness. The depression subscale of the RCADS has high validity and reliability in both the clinical and nonclinical population (21,22). For the purposes of the current study, one item was excluded from analysis as this item measures fatigue. In order to account for the excluded item, all raw scores were divided by 9 and multiplied by 10. Raw scores from the RCADS were then converted into T-scores, which are age- and gender-adjusted scores. A T-score of ≥65 indicates possible clinical depression (23). In the current study, the RCADS depression subscale had a high internal consistency, with an alpha coefficient of 0.86.

Anxiety: The 6-item generalised anxiety subscale of the RCADS asks about the tendency to worry about things, worrying about bad things happening to oneself or family members, and thinking about death. Raw scores for this RCADS subscale were converted to T-scores (as described above). A T-score of ≥65 indicates possible clinical anxiety (23). The general anxiety subscale of the RCADS has been shown to have a high validity and reliability in clinical and nonclinical populations

(21,22). The RCADS (anxiety subscale) had a high internal consistency, with an alpha coefficient of 0.89.

The measures were not available in Afrikaans. At the outset of the study, the research assistant, an Afrikaans speaking master's student, translated these questionnaires from English to Afrikaans, and the accuracy of the translation was checked by a senior member of the research team (BC).

Ethical considerations: We obtained ethical approval for this study from the Stellenbosch University Research Ethics Committee (#HREC N16/03/032) and the Western Cape Department of Health. Participants were asked to complete an informed consent form and were assured of confidentiality of their data. All participants gave written informed consent. Since most of the participants attended the consultation without a parent/caregiver, we received ethics clearance for a parental waiver of consent.

Data analysis: The data were analysed using the Statistical Package for Social Sciences (SPSS), version 24. The data were checked for normality and outliers, and positively skewed variables (depression and insomnia) were corrected with log transformations. We calculated Cronbach's alpha for each measure to determine internal consistency, which are reported where each measure has been described in the methods. We used descriptive statistics (frequencies, percentages, means, and standard deviations) to summarise the data pertaining to demographic and symptom characteristics. Further, we used an independent sample t-test to compare male and female participants' scores on fatigue, insomnia, depression, and anxiety. We

calculated bivariate correlations amongst age, gender, fatigue, insomnia, depression, and anxiety. Variables that significantly correlated with fatigue were then entered into a hierarchical regression model, with fatigue as the outcome variable. Predictors were added to the regression model in blocks, where block 1 contained demographic variables (age, gender), and block 2 and 3 contained psychosocial variables, i.e. depression and insomnia, respectively.

Results

Demographic characteristics of the sample

A total of 134 adolescents (78 female; 56 male) participated in the study. The mean age was 14.3 (SD = 1.9) years and participants identified as either coloured (N = 24; 17.9%) or Black (N = 110; 82.1%). All participants, except for one, were attending school. In terms of social class, participants identified as either lower- (N = 94; 70.1%), working- (N = 38; 28.4%), or middle-class (N = 2; 1.5%). There were no significant differences ($p>.05$) between male and female participants on these variables.

Symptom characteristics of study participants

Applying thresholds from the existing literature, each of the measures identified a proportion of participants who reported clinically significant symptoms; 24.6% (n=33) fatigue, 20.1% (n = 27) insomnia, 9.7% (n = 13) depression and 6.7% (n = 9) anxiety

(see Table II). Further, female participants scored significantly higher ($p = <.05$) on insomnia, and symptoms of depression compared to male participants.

<Insert table II about here>

Bivariate correlations

As can be seen in Table III, age, depression and insomnia all correlated significantly with fatigue. These variables were moderately and positively correlated with one another.

<Insert table III about here>

Regression diagnostics

The various regression diagnostics, including the Cook's and Mahalanobis distances, and variance inflation factors were within the acceptable range for regression analysis.

Predicators of fatigue

Table IV presents the regression model summary with fatigue as the criterion/outcome variable. The linear combination of the predictors, namely age, gender, depression and insomnia explained 40.6 % of the variance in fatigue. Table V shows that age, depression and insomnia were each unique and significant predictors of fatigue.

<Insert table IV about here>

<Insert table V about here>

Discussion

To our knowledge, this is the first study to report on the correlates and predictors of fatigue amongst HIV-infected adolescents. Our previous qualitative work with 14 HIV-infected adolescents with fatigue showed the disruptive impact of fatigue on concentration at school and illustrated how fatigue can be a barrier to interacting with peers (11). The current study has further highlighted the presence of fatigue among a subsample of adolescents living with HIV, and has indicated how the symptom experience of fatigue may be linked to other symptoms, including mental health.

We found that around a quarter (24.6%) of adolescents were experiencing clinically significant fatigue, with one in five experiencing insomnia and one in ten reporting possible depression. Notably, fewer adolescents reported symptoms of depression and insomnia compared to fatigue. The difference in the rates between depression, insomnia and fatigue is important to note, given the considerable overlap between symptoms of fatigue, depression and insomnia (6). Despite this overlap, studies show that fatigue presents independently of depression, and insomnia (9) as was the case in our study (6,14,24). Indeed, participants in our study were more likely to report fatigue than depression, indicating that depression alone cannot account for all fatigue experienced by those living with HIV, which is consistent with other existing findings in adults (5). This finding also demonstrates that targeted interventions aimed at addressing fatigue as a primary outcome are necessary and important.

Our findings showed that older adolescents, those with higher levels of depressive symptoms, and those with more problems with sleep, were more likely to also be fatigued. These findings are echoed in the adult literature (6,7,15). Notably, insomnia was moderately positively correlated with fatigue. In their study, Low et al (2013) demonstrated that even when controlling for depression, insomnia remained a significant predictor of fatigue among adults with HIV, and that this relationship persisted when controlling for biological markers such as CD4 count. Research is needed to explore the relationship between biological markers (such as CD4 count and viral load) and fatigue in adolescents living with HIV.

We showed that, in linear combination, all of the variables, except gender, explained a substantial amount of the variance in fatigue. In the literature there are mixed results as to whether gender is predictive of fatigue. While some studies in adults with HIV have shown female gender to be associated with fatigue (9), others have found no association between the two (25). These differences may be attributable to methodology, and in studies where other potential confounding variables have been controlled for, the apparent association between gender and fatigue disappears.

The literature demonstrates that failure to ameliorate symptoms of fatigue among adults living with HIV affects adherence to ART (26–28) and the same may be true for adolescents, given the rates of fatigue found in the current study. Further, the literature demonstrates that fatigue in adults with HIV does not remit spontaneously over time and if left untreated, symptoms of fatigue may worsen (6). Again, this may be true of adolescents. As mentioned, we identified clinically significant symptoms of depression in around one in ten adolescents with HIV in our sample. This finding is comparable to prevalence rates of depression found in other

samples of adolescents in South Africa (29,30). However, as depression symptoms also contribute to non-adherence to ART in adults with HIV (31), mood is another important factor to bear in mind, consistent with the symptom management model that highlights the inter-relations between different factors in symptom perpetuation and management. Early-detection of fatigue (and indeed depression) amongst adolescents with HIV may be achievable within schools settings. For example, our previous qualitative work with HIV-infected adolescents who reported fatigue, reported poor concentration and social withdrawal (11). As such, it may be worthwhile exploring the feasibility of equipping school staff with the necessary skills to identify these symptoms and make appropriate referrals,

In addition to highlighting areas for future research, these findings highlight the importance of identifying and treating fatigue as soon as it is reported or observed amongst adolescents. A measurement tool such as the Chalder Fatigue Questionnaire (CFQ) is easy to administer, cost-effective, and has shown reliability amongst HIV-infected adolescents (8). The CFQ may be a useful tool to incorporate in clinical settings as part of routine care and symptom management in order to identify adolescents with symptoms of fatigue.

While our study has explored the symptom experience of fatigue in this population, it has some limitations. Firstly, we recruited consecutive clinic attenders at two healthcare facilities in the Western Cape, which limits generalizability to other settings. Secondly, our study was cross-sectional, which limits any causal inference from our findings. Future studies would benefit from longitudinal designs to better understand the severity of fatigue among adolescents living with HIV over time and in particular, throughout adolescence and into adulthood. Thirdly, we did not collect data on income, or average household income, which is known to influence fatigue in

the adult HIV literature. For example, studies have shown that low income and unemployment are associated with higher levels of fatigue (5,15). Finally, we relied on self-report measures and did not include physiological data such as viral load, which would be important to collect in future studies.

Conclusion

Fatigue appears to be a symptom that is experienced among a considerable minority of adolescents living with HIV and is associated with sleep disturbance and with depression. Adolescents who experience elevated levels of fatigue may also be struggling with their mood and with maintaining their sleep, which may impact on their adherence to ART. However, as these factors did not fully account for fatigue, it is also important that future research explore other factors/biological markers which may contribute to fatigue, such as viral load. Given the disabling nature of fatigue amongst adolescents with HIV, there is a need to develop appropriate interventions to ameliorate these symptoms, and prevent these symptoms from escalating and interfering with adherence to ART, school completion, and retention in health care. This study has furthered the understanding of the fatigue experience in this population, which has implications for symptom identification and management.

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Table I. Table summarising evidence of factors associated with fatigue in adults living with HIV

Factor Type	Factor	Evidence pertaining to an association with fatigue
Biological marker	CD4 count	Lower CD4 count associated with higher levels of fatigue (1–3). However, no evidence of an association was found in other studies (4–6).
	Viral load	Higher viral loads associated with increased fatigue (7). However, no evidence of an association was found in other studies (6,8,9).
Sociodemographic	Age	Fatigued persons with HIV have been shown to be younger than non-fatigued persons with HIV(10).
	Gender	Women are more likely to have higher levels of fatigue (6).
	Income/employment status	Inadequate income and unemployment are associated with higher levels of fatigue (11).
Psychosocial	Depression	Higher levels of depressive symptoms/depression are associated with higher levels of fatigue (4–6,8).
	Anxiety	Fatigue is associated with state and trait anxiety (8). Increases in anxiety, stress and depression have been shown to increase fatigue (12).
	Insomnia	Those participants who reported higher levels of sleep problems also reported higher levels of fatigue (13).

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Table II: Symptom characteristics of study participants by gender

Variable	Cut-offs	% scoring above cut-off	Male (N = 56)		Female (N = 78)		t	*p*
			Mean	SD	Mean	SD		
Fatigue	≥18 on CFQ	24.6	14.12	3.89	15.42	3.71	-1.93	0.06
Insomnia	≥7 on AIS	20.1	3.07	2.98	4.54	3.54	-2.53	0.01*
Depression	≥65 on RCADS	9.7	42.02[a]	9.24	46.63[a]	13.89	-2.16	0.03*
Anxiety	≥65 on RCADS	6.7	41.84[a]	10.92	45.38[a]	13.84	-1.59	0.11

***p ≤ 0.05**

[a] Adjusted T-scores were used for analysis

Table III. Bivariate correlation matrix of variables

	Age	Fatigue	Depression	Insomnia	Anxiety
Age	1				
Fatigue	**.325****	1			
Depression	.174*	**.502****	1		
Insomnia	.272**	**.538****	.444**	1	
Anxiety	.239**	.158	.514**	.232**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table IV. Model summary with fatigue scores (Likert scores) as dependant variable

Model	R	R Square	Adjusted R Square	Std. Error of the estimate
1	.375a	.141	.127	3.57246
2	.566b	.321	.305	3.18826
3	.637c	.406	.387	2.99313

a Predictors: Gender, Age

b Predictors: Gender, Age, Depression

c Predictors: Gender, Age, Depression, Insomnia

Table V. Predictors of fatigue (CFQ)

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	3.319	2.522		1.316	.190
	Age	.647	.156	.337	4.152	.000
	Gender	1.451	.627	.188	2.314	.022
2	(Constant)	-18.636	4.364		-4.270	.000
	Age	.491	.142	.255	3.463	.001
	Gender	.824	.570	.107	1.446	.151
	Depression	15.399	2.623	.439	5.872	.000
3	(Constant)	-10.922	4.472		-2.442	.016
	Age	.348	.137	.181	2.539	.012
	Gender	.365	.545	.047	.669	.505
	Depression	10.904	2.675	.311	4.076	.000
	Insomnia_	4.104	.954	.341	4.301	.000